General

Guideline Title

Neurological problems in liver transplantation.

Bibliographic Source(s)

Guarino M, Benito-Leon J, Decruyenaere J, Schmutzhard E, Weissenborn K, Stracciari A. Neurological problems in liver transplantation. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 491-9. [84 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Guarino M, Benito-Leon J, Decruyenaere J, Schmutzhard E, Weissenborn K, Stracciari A, EFNS. EFNS guidelines on management of neurological problems in liver transplantation. Eur J Neurol 2006 Jan;13(1):2-9.

Recommendations

Major Recommendations

The levels of evidence (Class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point [GPP]) are defined at the end of the "Major Recommendations" field.

Immunosuppression Neurotoxicity

Cyclosporine (CS) and Tacrolimus Neurotoxicity

Prevention requires minimum efficacious doses, oral administration as soon as possible, strict monitoring of plasma levels (including metabolites), electrolyte imbalance (e.g., hypomagnesaemia), hypertension check and correction, and attention to pharmacological interactions (Level C). Brain magnetic resonance imaging (MRI) is the choice diagnostic tool (Level B) and should be performed as soon as severe neurotoxicity is suspected (GPP). In case of major side effects, prompt switching to a non-calcineurin inhibitor (e.g., sirolimus) is indicated (GPP). Secondary options include conversion from CS to tacrolimus and vice versa (GPP). Minor complications require switching only in case of intractable and invalidating symptoms. Generally, their treatment should follow the guidelines for these disorders, administering drugs lacking both hepatotoxicity and interference with immunosuppressants (e.g., gabapentin for paraesthesias, riboflavin for migraine prophylaxis) (GPP).

OKT3 Neurotoxicity

Prevention consists of administering minimal dosages and premedication with corticosteroids (GPP). Aseptic meningitis does not need treatment,

because it is usually self-limiting. Encephalopathy requires antioedema agents and very rarely OKT3 withdrawal (GPP).

Corticosteroid Neurotoxicity

Severe acute behavioural disorders may be treated by a temporary reduction and/or withdrawal of intravenous steroid administration. Brief regimens of low-dose neuroleptics may be considered (GPP).

Seizures

Seizure prevention requires close monitoring of metabolic parameters and immunosuppressant levels, and caution in managing discontinuation or adjustment of epileptogenic drugs (GPP). The diagnostic approach should routinely include laboratory tests, electroencephalogram (EEG) and neuroimaging. Cerebrospinal fluid (CSF) examination is indicated when central nervous system infection is suspected (GPP). Brain MRI is the current standard of reference (Level B). When MRI is not available or contraindicated, computerized tomography (CT) can be applied (Level C).

The first-line intravenous antiepileptic drug is levetiracetam at a dose of 500 mg twice daily (up to 1000 mg twice daily) (Class IV). Alternatively, phenytoin could be used, dosed to target a level between 10 and 20 μg/ml (GPP). When oral administration is possible, gabapentin, pregabalin, or levetiracetam should be considered (GPP). Status epilepticus must be managed according to guidelines for the general population (GPP). In most cases, antiepileptic therapy can be suspended after 3 months (Level C).

Central Pontine Myelinolysis

Given enough time before liver transplantation (LT), hyponatremia should be corrected slowly. The variations in serum sodium concentration must be carefully monitored and controlled before and during surgery to avoid major fluctuations (GPP). If the patient is hyponatremic when undergoing LT, a perioperative hourly correction rate at or below 0.5 mM/L per hour should be maintained. The correction rate should not exceed 8 mM/L per day (GPP). MRI should be performed early and repeated if negative (GPP).

Neuromuscular Disorders

Perioperative Mononeuropathies

Prevention implies caution during catheterization, and avoiding blinded cannulations and external compressions by blood pressure cuffs or tourniquets (GPP). To reduce perioperative malpositioning, it is indicated to maintain the arms at less than 90º of abduction, to maintain the arms at less than 30º of extension when combined with abduction, padding of the exposed nerves (i.e., at the level of fibular head, popliteal space, calcaneus, under forearms, under hands) with frequent repositioning during prolonged surgery. Patients should be instructed to avoid postures potentially compressing or stretching the nerves (GPP).

Generalized Weakness

Prevention requires avoiding, when possible, the prolonged use of non-depolarizing neuromuscular blocking agents and minimizing the use of high-dose intravenous corticosteroids (Level C). In case of calcineurin inhibitor toxicity, prompt switching to a different agent (e.g., sirolimus) is recommended (GPP). Customary general treatment for critical illness and conventional management of Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy are indicated (Level B).

Cerebrovascular Disorders

Prevention includes correction of coagulopathies before surgery (e.g., administration of platelets and blood products but with caution because of the risk of consumptive coagulopathy), avoiding perioperative cerebral hypoperfusion and control of cerebrovascular risk factors after LT (especially hypertension) (GPP). According to general guidelines, CT scan is the preferred diagnostic test in early phases of acute cerebrovascular disorders, especially to detect haemorrhage (Level C). Despite its greater sensitivity, MRI is often not tolerated or is not applicable immediately after LT, but it should be considered to characterize some vascular lesions or to rule out other aetiologies (GPP).

A search for bacteremia or fungaemia to detect infection should be routinely applied (GPP). The general treatment of cerebrovascular disorders in LT should not differ from that applied in the general population (GPP). Concomitant antifungal treatment should be given in the presence of angiopathy related to central nervous system (CNS) infections (Level C).

CNS Infections

An early in-depth diagnostic approach is advocated, including brain CT/MRI, lumbar puncture and possibly brain biopsy, and the search for extracerebral sources of infection (GPP). CSF polymerase chain reaction is essential for viral infections (Level A). Prompt administration of therapy on suspicion of the diagnosis without definitive proof is needed to control infection (GPP). An exhaustive search for latent infection in donor and recipients is required, including close monitoring for intestinal strongyloidiasis in patients who have lived for long periods in tropical or

subtropical countries (Level C). Exposure to hospital contamination must be avoided (Level C). Specific drug protocols to prevent brain infections are not required (GPP).

Treatment of neurolisteriosis consists of prolonged administration of ampicillin intravenously; the second choice includes trimethoprim-sulfamethoxazole (Level C). For brain nocardiosis, prolonged administration of trimethoprim–sulfamethoxazole is suggested (Level C).

For brain aspergillosis, the first-choice drug is voriconazole: initially, 6 mg/kg intravenously every 12 h in two doses, then 4 mg/kg intravenously every 12 h, switching to oral dosing (the same dosage) as tolerated and clinically justified; the maintenance regimen consists of 200 to 300 mg orally every 12 h. The duration of intravenous therapy should be between 6 and 27 days, followed by oral administration for 4 to 24 weeks (Level A). In case of intolerance, contraindications, or therapy failure, use liposomal amphotericin B (1 to 5 mg/kg per day) or caspofungin 50 mg/day (with a loading dose of 70 mg on day 1) or itraconazole (except after voriconazole) (Level B). Surgical resection may be considered. Rhinocerebral mucormycosis needs maximally dosed liposomal amphotericin B (5 to 10 mg/kg per day).

First-line treatment for cryptococcal meningitis is a combination of liposomal amphotericin B plus 5-flucytosine. Schedule treatment includes: induction with amphotericin B (0.7 mg/kg per day) and flucytosine (150 mg/kg per day) for 2 weeks, followed by consolidation with fluconazole for 8 to 10 weeks (400 to 800 mg/day), followed by 6 to 12 months at lower doses of fluconazole (200 mg/day) (Level A). Treatment for herpesvirus-6 and cytomegalovirus encephalitis is ganciclovir and foscarnet, either alone or in combination (Level C). For progressive multifocal leukoencephalopathy, cidofovir is a possible option (GPP).

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent,

convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point Clinical areas exhibiting class IV scientific evidence for which consensus could be reached were indicated as Good Practice Points (GPP).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Neurological impairment after orthotopic liver transplantation (LT), including:

- Immunosuppression neurotoxicity
- Seizures
- Central pontine myelinolysis (CPM)
- Neuromuscular disorders
- Cerebrovascular disorders
- Central nervous system infections

Guideline Category

Diagnosis

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Infectious Diseases

Internal Medicine

Neurology

Preventive Medicine

Surgery

Intended Users

Hospitals

Physicians

Guideline Objective(s)

To update and revise the previous guidelines for prevention, diagnosis, and management of problems emerging in the first 6 months after orthotopic liver transplantation (LT)

Target Population

Patients with or at risk for neurological problems after orthotopic liver transplantation

Interventions and Practices Considered

Prevention

1. Monitoring and control of plasma levels, electrolytes, hypertension, immunosuppressant levels, serum sodium concentration
2. Attention to pharmacologic interactions
3. Administering minimum efficacious dose of immunosuppressants
4. Premedication with corticosteroids
5. Caution in managing drugs and procedures (e.g., catheterization)
6. Control of risk factors

Diagnosis

1. Brain magnetic resonance imaging (MRI)
2. Computed tomography (CT)
3. Cerebrospinal fluid (CSF) examination and polymerase chain reaction (PCR)
4. Electroencephalogram (EEG)
5. Neuroimaging
6. Lumbar puncture
7. Brain biopsy
8. Laboratory tests

Treatment

1. Switching to non-calcineurin inhibitor (e.g., sirolimus)
2. Reduction or withdrawal of intravenous steroids
3. Antioedema agents
4. Low-dose neuroleptics
5. Antiepileptic drugs
6. Antifungal, antibiotic, or antiviral medication, as indicated

Note: See the "Major Recommendations" field and the original guideline document for management recommendations for specific neurological impairments.

Major Outcomes Considered

- Incidence of neurological disorders in liver transplantation
- Effectiveness of management

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Each member of the task force was assigned one of the six selected topics and systematically reviewed the relevant literature through the Medline database of the National Library of Medicine from January 2005 to June 2009, the Cochrane Library, existing guidelines (National Guideline Clearinghouse, Scottish Intercollegiate Guidelines Network, National Institute of Clinical Excellence) and textbooks.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a 'gold standard' for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by 'gold standard') compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias

e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Data collection and analysis of evidence was performed independently by each participant according to the assignment.

The literature is analysed giving the class of evidence (I–IV) according to EFNS guidelines (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

In 1999, a task force was set up under the auspices of the European Federation of Neurological Societies (EFNS) to devise guidelines to prevent and manage neurological problems in liver transplantation (LT). The task force members considered six key topics in clinical practice: immunosuppression neurotoxicity, seizures, central pontine myelinolysis (CPM), neuromuscular disorders, cerebrovascular disorders, and central nervous system (CNS) infections.

On the basis of the single reports, one of the task force members produced a first draft of the updated guidelines, which was then submitted several times for the approval of all the members until any discrepancies on each topic were solved and a consensus was reached.

The recommendation section includes statements classified in Levels A to C derived from Classes I–III of evidence according to EFNS guidelines when feasible (see the "Rating Scheme for the Strength of the Evidence" and "Rating Scheme for the Strength of the Recommendations" fields). For those clinical areas exhibiting Class IV scientific evidence, recommendations were based on the agreement obtained and indicated in the text as Good Practice Points (GPP).

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point Clinical areas exhibiting class IV scientific evidence for which consensus could be reached were indicated as Good Practice Points (GPP).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

The recommendation section includes statements classified in levels A to C derived from Classes I–III of evidence according to EFNS guidelines when feasible (see the "Availability of Companion Documents" field). For those clinical areas exhibiting Class IV scientific evidence, recommendations were based on the agreement obtained and indicated in the text as Good Practice Points (GPP).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate prevention, diagnosis, and treatment of neurological disorders after liver transplantation

Potential Harms

- Administration of platelets and blood products for correction of coagulopathies should be done with caution due to the risk of consumptive coagulopathy.
- Oral doses of gabapentin, pregabalin, and levetiracetam should be reduced in patients with concomitant renal dysfunction, while in patients on dialysis supplemental doses must be given after dialysis. Some antiepileptic drugs can produce clinically relevant interactions with the immunosuppressants used after liver transplantation.
- Minor side effects of immunosuppressive treatment are usually transient and self-limiting. Headache, tremor, paraesthesiae, and insomnia are successfully managed with symptomatic conventional treatment. However, a change in the immunosuppressive regimen has occasionally been necessary in refractory headache.

Qualifying Statements

Qualifying Statements

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Guarino M, Benito-Leon J, Decruyenaere J, Schmutzhard E, Weissenborn K, Stracciari A. Neurological problems in liver transplantation. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 491-9. [84 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2006 Jan (revised 2011)

Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

Source(s) of Funding

European Federation of Neurological Societies

Guideline Committee

European Federation of Neurological Societies Task Force on Neurological Problems in Liver Transplantation

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Financial Disclosures/Conflicts of Interest

The task force members declare that they have no conflict of interest in connection with this paper.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies (EFNS) Web site .

Availability of Companion Documents

The following is available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on December 8, 2006. The information was verified by the guideline developer on January 2, 2007. This summary was updated by ECRI Institute on October 2, 2007, following the U.S. Food and Drug Administration (FDA) advisory on Haloperidol. This summary was updated by ECRI Institute on May 1, 2009 following the U.S. Food and Drug Administration advisory on antiepileptic drugs. This summary was updated by ECRI Institute on August 18, 2009, following the revised FDA advisory on CellCept (mycophenolate mofetil). This summary was updated by ECRI Institute on January 26, 2010 following the U.S. Food and Drug Administration advisory on Rapamune (sirolimus). This summary was updated by ECRI Institute on May 20, 2011 following the U.S. Food and Drug Administration advisory on antipsychotic drugs. This NGC summary was updated by ECRI Institute on February 20, 2012.

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